Brain Drain?

PBDEs Alter Development of Human Brain Cells

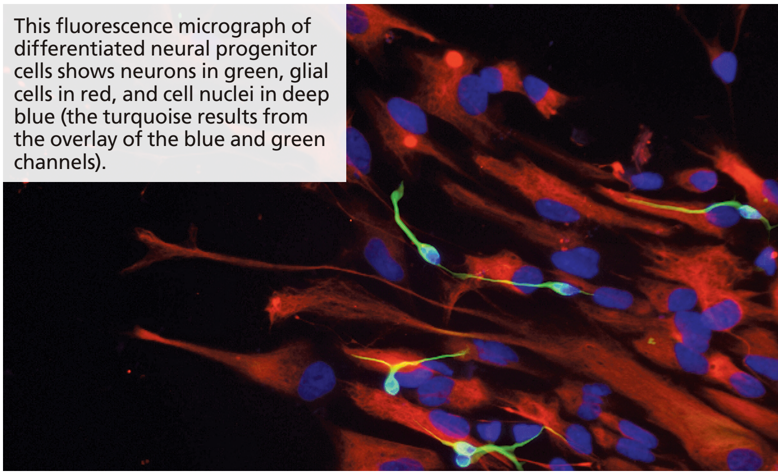
A new laboratory study demonstrating that polybrominated diphenyl ethers (PBDEs) can alter human fetal brain cells may explain at least in part the neurotoxicity recently documented in epidemiologic studies of young children exposed to PBDEs and previously shown in animal models [***EHP*** **118:572–578; Schreiber et al.**]. The new study, the first to examine PBDE neurotoxicity in a human cell–based system, links the brain cell alterations to endocrine disruption.

A wealth of data demonstrates that babies can be exposed to significant amounts of PBDE flame retardants both in the womb and through breastfeeding. Although all 3 PBDE formulations—penta, octa, and deca—are banned in Europe, and the penta and octa formulations were discontinued in the United States (deca also is banned in some states), PBDEs may still be used in some new U.S. products and in wares manufactured elsewhere. They also are found in a wide variety of older plastic consumer goods that remain in use in many homes, businesses, and automobiles. The PBDEs are known to migrate into indoor dust, posing a particularly high exposure risk to infants and toddlers because of their characteristic hand-to-mouth behavior.

To investigate how PBDEs may impact the developing fetal brain, the team of scientists employed a method for evaluating human developmental neurotoxicity they had recently developed [*EHP* 117:1131–1138] as an alternative to animal testing. This method uses primary fetal human neural progenitor cells (hNPCs) cultured to produce complex 3-dimensional cellular systems called neurospheres. Neurospheres undergo the same basic processes that occur during the early stages of normal human brain development: cell proliferation, differentiation, and migration. Tests conducted with neurospheres may help identify exogenous substances that disturb these basic processes *in vivo*.

The researchers focused on 2 of the PBDE compounds that accumulate the most in humans, BDE-47 and BDE-99. At concentrations below levels that cause cell death, they found these compounds could reduce the migration of the hNPCs—which suggests the possibility of adverse effects on brain development—and the effects increased with higher PBDE concentrations. At the highest tested concentration (10 µM), BDE-47 decreased the distance the cells migrated by more than 25% compared with unexposed cells, whereas the same concentration of BDE-99 decreased the distance by more than 30%. Additional testing established that both compounds also interfered with the differentiation of immature progenitor cells into neurons and oligodendrocytes.

Further tests suggested the PBDE compounds affected cell migration and differentiation by interfering with thyroid hormone signaling, an endocrine-disrupting effect that could be associated with additional impacts throughout a person's life. Followup work to determine whether PBDEs cause the same effects in rodent neurospheres would facilitate extrapolation from animals to humans, the authors say.



This fluorescence micrograph of differentiated neural progenitor cells shows neurons in green, glial cells in red, and cell nuclei in deep blue (the turquoise results from the overlay of the blue and green channels).

Other work has shown the tendency of PBDEs to accumulate in brain and neuronal cells, and the researchers used radiolabeled BDE-47 to measure an accumulation in test cells of approximately 60-fold. Considered with available human exposure data, these data suggest current PBDE exposure levels are likely to be of concern for human health, the authors write. Two recent studies have linked PBDEs with subtle changes in childrens' IQs and behavior [*EHP* 117:1953–1958 and *EHP* doi:10.1289/ehp.0901340], and the authors say additional studies are needed to assess these associations.

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Chew on This

Persistent Organic Pollutants May Promote Insulin Resistance Syndrome

Animal studies indicate some persistent organic pollutants (POPs) may be endocrine disruptors and suggest similar health risks for humans. Recent studies have further suggested an association between exposure to POPs and the prevalence of type 2 diabetes. Now an experimental animal study reports evidence of a causal link between POP exposure and insulin resistance syndrome, a cluster of metabolic disorders—including type 2 diabetes—that are marked by sustained high blood sugar [***EHP*** **118:465–471; Ruzzin et al.**].

POPs accumulate in fatty tissue, where they can remain for years because they are not easily broken down. Fatty fish are a potential source of POP exposure in many human populations. However, *n*-3 polyunsaturated fatty acids in fish oil may have beneficial health effects, possibly including protective effects on insulin resistance, that could counterbalance any adverse effects of POPs in fatty fish.

In the current study, rats were exposed for 28 days to high-fat diets that contained either crude fish oil (from farmed Atlantic salmon) or fish oil that was refined to remove POPs. As expected, the crude fish oil contained much higher levels of POPs than the refined oil. Gene expression profile comparisons of the livers of the 2 treatment groups showed that POP exposure disrupted lipid homeostasis.

Rats on the unrefined fish oil diet gained more weight overall and had increased triacylglycerol, diacylglycerol, and total cholesterol levels compared with rats fed refined fish oil. They also showed impaired insulin action in response to the high-fat diet, whereas the high-fat diet did not seem to cause insulin resistance in the rats fed refined fish oil. Further analysis revealed a reduction in the ability of insulin to stimulate glucose uptake in adipocytes treated with a mixture of POPs that was comparable to the mixture of chemicals in crude fish oil. Adipocyte responses to insulin varied with exposures to different mixtures of individual POPs.

The authors conclude that dietary exposure to POPs may be a risk factor for insulin resistance and associated metabolic disorders. Furthermore, the metabolic effects of POP exposures exacerbated deleterious effects of a high-fat diet on rats and appeared to negate protective effects of *n*-3 polyunsaturated fatty acids on insulin resistance.

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